REMARKS

The Official Action dated June 17, 2002 has been carefully considered. Accordingly, the CPA Request Transmittal and the changes presented herewith, taken with the following remarks, are believed sufficient to place the present application in condition for allowance. Reconsideration is respectfully requested.

By the present Amendment, claims 31 and 52 are cancelled. Claims 27, 28, 53, 55 and 60 are amended to clarify the limitations therein, generally in accord with the Examiner's suggestions. Further, claims 27, 28, 53-55, 60 and 62 are amended to replace the word "eukaryotic" with "mammalian" in accordance with the teachings of the specification at page 4, lines 1-3. A Version With Markings Showing Changes Made is attached. Claims 64 and 65 are added. Support for these claims may be found throughout the specification, particularly at page 1, lines 19-22. It is believed that these changes do not involve any introduction of new matter, whereby entry is believed to be in order and is respectfully requested.

Claims 27, 28, 31-50 and 52 have been objected to for being drawn to non-elected inventions. The Examiner asserted that even though the claims are drawn to "mediating transgenic recombination", they are not limited to the elected invention of methods of genetic modification in animals. This objection is traversed and reconsideration is respectfully requested.

More particularly, claims 27 and 28 recite methods for mediating transgenic intramolecular recombination selected from deletions of DNA sequence located between two *six* sites and inversions of DNA sequences located between two *six* sites, in mammalian cells (claim 27) or in chromatin structures of mammalian cells (claim 28). Claim 43 recites methods for catalyzing site-specific resolution of DNA sequence located between *six* sites in

an extrachromosomal substrate transfected into a mammalian cell. Since mammalian cells do not encompass plant or prokaryotic cells, the elected claims do not encompass Group II or Group III claims. Moreover, as the methods are drawn to genetic modification in mammalian cells and not to gene therapy, the claims do not encompass Group IV claims. Applicants also note that claim 34 was cancelled in a previously entered Amendment and thus, is not a claim under consideration. Accordingly, it is believed that this objection has been overcome. Reconsideration is respectfully requested.

Claims 27, 28, 31-33, 35-50 and 52-63 were rejected under 35 U.S.C. §112, first paragraph, as not being enabled by the specification. The Examiner asserted that while the specification is enabling for a method of mediating intramolecular recombination between two *six* sites in a mouse, the specification is not enabling for all other animals. In addition, the Examiner asserted that at the time of filing this application, the methodology of Cre and Flp had not been successfully used in other animal models, such as pigs. Further, the Examiner asserted that while the specification clearly teaches that cofactors are necessary for beta recombinase to mediate a recombination event, the specification is silent on the effective amounts of these cofactors and whether HMG1 or a functional homolog exists in species other than mammals.

However, as will be set forth in detail below, Applicants submit that the methods defined by claims 27, 28, 31-33, 35-50 and 52-63 are fully enabled to one of ordinary skill in the art, in accordance with the requirements of 35 U.S.C. §112, first paragraph. Accordingly, this rejection is traversed and reconsideration is respectfully requested.

More particularly, according to claim 27, the invention is directed towards methods for mediating transgenic intramolecular recombination selected from deletions of DNA sequences located between two *six* sites and inversions of DNA sequences located between

two *six* sites, in mammalian cells. The methods comprise the step of transfecting mammalian cells with prokaryotic beta recombinase and DNA sequences containing *six* sites that allow recombination activity. The prokaryotic beta recombinase is capable of using factors provided by the mammalian cells in order to mediate recombinase activity.

According to claim 28, the invention is directed towards methods for mediating transgenic intramolecular recombination selected from deletions of DNA sequences located between two *six* sites and inversions of DNA sequences located between two *six* sites, in chromatin structures of mammalian cells. The methods comprise the step of transfecting mammalian cells with prokaryotic beta recombinase and DNA sequences containing *six* sites that allow recombination activity. The prokaryotic beta recombinase is capable of using factors provided by the mammalian cells in order to mediate recombinase activity.

According to claim 43, the invention is directed towards methods for catalyzing site-specific resolution of DNA sequences located between *six* sites in an extrachromosomal substrate transfected into a mammalian cell. The methods comprise the step of catalyzing the site-specific resolution with beta recombinase. The mammalian cell provides factors which beta recombinase is capable of using in order to mediate recombinase activity.

According to claim 53, the invention is directed towards methods for mediating transgenic intramolecular recombination in mammalian cells. The methods comprise the step of transfecting mammalian cells with prokaryotic beta recombinase and DNA sequences containing the *six* sites that allow recombination activity. The prokaryotic beta recombinase is capable of using factors provided by the mammalian cells in order to mediate recombinase activity. The factors provided by the mammalian cells comprise HMG1 chromatin-associated protein.

According to claim 55, the invention is directed towards methods for mediating transgenic intramolecular recombination in chromatin structures of mammalian cells. The methods comprise the step of transfecting mammalian cells with prokaryotic beta recombinase and DNA sequences containing *six* sites that allow recombination activity. The prokaryotic beta recombinase is capable of using factors provided by the mammalian cells in order to mediate recombinase activity. The factors provided by the mammalian cells comprise HMG1 chromatin-associated protein.

Finally, according to claim 60, the invention is directed towards methods of mediating beta recombinase activity. The methods comprise the step of transfecting mammalian cells with beta recombinase and DNA sequences containing *six* sites that allow recombination activity. The beta recombinase is capable of using mammalian cell factors of the mammalian cell to mediate recombinase activity.

Applicants note that claim 58 has been cancelled in a previously entered Amendment and thus, is not a claim under consideration.

In summary, the methods of claims 27, 28, 53 and 55 are directed towards meditating transgenic intramolecular recombination. The methods of claim 43 are directed towards catalyzing site-specific resolution, i.e., intramolecular recombination, of DNA sequences located between *six* sites in an extrachromosomal substrate transfected into a mammalian cell. Finally, the methods of claim 60 are directed towards mediating beta recombinase activity, i.e., intramolecular recombination mediated by the beta recombinase protein. These methods expand the site-specific recombinase art by using beta recombinase for mediating intramolecular recombination reactions between *six* sites in a mammalian cell.

Applicants note that even though the present methods may be useful in the generation of transgenic animals, claims 27, 28, 31-33, 35-50 and 52-63 recite methods of

intramolecular recombination events in mammalian cells. Manipulation of mammalian genomes, specifically the method of transfecting a protein, such as beta recombinase, or a DNA substrate, into a mammalian cell is known to one of ordinary skill in the art. Moreover, the specification of the present invention at page 5, lines 12-20 and page 9, lines 3-30 illustrates working examples, in which beta recombinase and/or a DNA substrate containing two *six* sites have been transfected into simian COS1-1 mammalian cells. Therefore, the claims of the present invention are fully enabled by the specification and to one of ordinary skill in the art.

Finally, Applicants note that the specification at page 16, lines 17-18 disclose that HMG1 and/or HMG2 chromatin associated proteins found in mammalian cells can effectively stimulate beta-mediated recombination in mammalian cells. Therefore, since the beta recombinase is capable of using chromatin cofactors, such as HMG1 and HMG2, provided by the mammalian cell to mediate recombinase activity, there is no requirement to provide cofactors to the cell.

A disclosure is enabling if, from the information set forth in the specification, coupled with information known in the art, one of ordinary skill in the art could make and use the invention without undue experimentation, *United States v. Teletronics, Inc.*, 8 U.S.P.Q.2d 1217, 1224 (Fed. Cir. 1988). Moreover, every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification; rather, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. *Genetech v. Novo Nordisk, A/S,* 42 U.S.P.Q.2d 1001, 1005 (Fed. Cir. 1997). Furthermore, Applicants are not required to disclose every embodiment encompassed by their claims, even in an unpredictable art. *In re Angstadt,* 190 U.S.P.Q. 214 (CCPA 1976).

One of ordinary skill in the art will appreciate that various methods are known in the art to manipulate mammalian cells. As one of ordinary skill in the art will appreciate, when beta recombinase is isolated and specific DNA sequences containing *six* sites that allow recombination activity are identified, the disclosed and claimed methods are fully enabled for a mammalian cell. Accordingly, the specification enables the methods of claims 27, 28, 31-33, 35-50, 52-57, 59 and 60-63, as required by 35 U.S.C. §112, first paragraph. It is therefore submitted that the rejection under 35 U.S.C. §112, first paragraph, has been overcome. Reconsideration is respectfully requested.

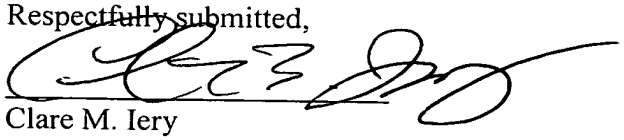
Claims 27, 28, 32, 53 and 55 were also rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner asserted that the claims have been amended to recite "modified version" that allow recombination activity, but the disclosure does not provide the necessary written description for what modifications of the natural sites can be made and still be functional. Specifically, the Examiner asserted that the only target sequence disclosed is the *six* site sequence and further, that the specification fails to describe any methods to establish any other sequence besides the *six* site.

This rejection is traversed and reconsideration is respectfully requested. However, in order to expedite prosecution, claims 27, 28, 53 and 55 have been amended to recite "DNA sequences containing *six* sites that allow recombination activity", thereby removing reference to the phrases "natural" and "modified versions". Applicants also note that claim 32 was not amended to recite "modified versions" and thus, is fully described by the specification. It is

therefore submitted that the rejection under 35 U.S.C. §112, first paragraph, has been overcome. Reconsideration is respectfully requested.

It is believed that the above represents a complete response to the objection and rejections under 35 U.S.C. §112, first paragraph, and places the present application in condition for allowance. Reconsideration and an early allowance are requested.

Respectfully submitted,



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VERSION WITH MARKINGS SHOWING CHANGES MADE

Claims 27, 28, 32, 43, 53, 54, 55, 60 and 61 are amended to read as follows:

27. (Fourth Amendment) A method for mediating transgenic intramolecular recombination selected from deletions of DNA sequences located between two *six* sites and inversions of DNA sequences located between two *six* sites, in [eukaryotic] mammalian cells, comprising the step of transfecting [eukaryotic] mammalian cells with prokaryotic beta recombinase and DNA sequences containing [the natural] *six* sites [or modified versions] that allow recombination activity; wherein the prokaryotic beta recombinase is capable of using factors provided by the [eukaryotic] mammalian cells in order to mediate recombinase activity.

28. (Fourth Amendment) A method for mediating transgenic intramolecular recombination selected from deletions of DNA sequences located between two *six* sites and inversions of DNA sequences located between two *six* sites, in chromatin structures of [eukaryotic] mammalian cells, comprising the step of transfecting [eukaryotic] mammalian cells with prokaryotic beta recombinase and DNA sequences containing [the natural] *six* sites [or modified versions] that allow recombination activity; wherein the prokaryotic beta recombinase is capable of using factors provided by the [eukaryotic] mammalian cells in order to mediate recombinase activity.

32. (Twice Amended) A method according to claim 27, wherein an intramolecular recombination between two *six* sites in [eukaryotic] mammalian cells is obtained.

43. (Third Amendment) A method for catalyzing site-specific resolution of DNA sequences located between *six* sites in an extrachromosomal substrate transfected into [an

eukaryotic] a mammalian cell, comprising the step of catalyzing the site-specific resolution with beta recombinase; wherein the [eukaryotic] mammalian cell provides factors which beta recombinase is capable of using in order to mediate recombinase activity.

53. (Third Amendment) A method for mediating transgenic intramolecular recombination in [eukaryotic] mammalian cells, comprising the step of transfecting [eukaryotic] mammalian cells with prokaryotic beta recombinase and DNA sequences containing [the natural] *six* sites [or modified versions] that allow recombination activity; wherein the prokaryotic beta recombinase is capable of using factors provided by the [eukaryotic] mammalian cells in order to mediate recombinase activity; and wherein the factors provided by the [eukaryotic] mammalian cells comprise HMG1 chromatin-associated protein.

54. (Amended) A method according to claim 28, wherein the factors provided by the [eukaryotic] mammalian cells comprise chromatin-associated protein.

55. (Third Amendment) A method for mediating transgenic intramolecular recombination in chromatin structures of [eukaryotic] mammalian cells, comprising the step of transfecting [eukaryotic] mammalian cells with prokaryotic beta recombinase and DNA sequences containing [the natural] *six* sites [or modified versions] that allow recombination activity; wherein the prokaryotic beta recombinase is capable of using factors provided by the [eukaryotic] mammalian cells in order to mediate recombinase activity; and wherein the factors provided by the [eukaryotic] mammalian cells comprise HMG1 chromatin-associated protein.

60. (Third Amendment) A method of mediating beta recombinase activity comprising the step of transfecting [eukaryotic] mammalian cells with beta recombinase and DNA sequences containing [the natural] *six* sites [or modified versions] that allow

recombination activity; wherein the beta recombinase is capable of using [eukaryotic] mammalian cell factors of the [eukaryotic cell] mammalian cells to mediate recombinase activity.

61. (Amended) A method according to claim 60, wherein the [eukaryotic] mammalian cell factors comprise HMG1 chromatin-associated protein.